

Genetics of Hypertensive Syndrome

Alejandro Martinez-Aguayo^a Carlos Fardella^b

^aEndocrinology Unit, Department of Pediatrics, and ^bDepartment of Endocrinology, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

Key Words

Hypertension · Aldosterone · Familial hyperaldosteronism · Liddle's syndrome · Glucocorticoid resistance · Congenital adrenal hyperplasia

Abstract

The knowledge of the genetic bases of hypertension has improved over the last decade; this area of research has high priority due to the high incidence of hypertension and its impact on public health. Monogenetic mineralocorticoid hypertension syndromes are associated with suppressed plasma renin activity due to excessive activation of the mineralocorticoid pathway. We review the pathophysiology, phenotype, and method of diagnosis for familial hyperaldosteronism type I and type II, hypertensive forms of congenital adrenal hyperplasia, 11 β -hydroxysteroid dehydrogenase type 2 deficiency, Liddle's syndrome, an activating mutation of the MR, and glucocorticoid resistance. We also review some genes that could contribute to essential hypertension.

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Introduction

Hypertension is the most prevalent, treatable risk factor for diseases of the heart, brain and kidneys. Available evidence suggests a major genetic impact on blood pres-

sure regulation. Existing evidence suggests that the genetic contribution to blood pressure variation is about 30–50% [1]. However, hypertension is a multifactorial disorder that probably results from the inheritance of a number of susceptibility genes and that involves multiple environmental determinants. The possible candidate genes are components of the renin-angiotensin-aldosterone system, adducin, β -adrenoceptors, G protein subunits, regulators of G protein signaling (RGS) proteins, rho kinases, and G protein receptor kinases (OMIM; #145500).

Inherited hypertension disorders may be mild, and electrolyte and acid-base abnormalities are often not present. Monogenic hypertension should therefore be included in the differential diagnosis of any child or adolescent with hypertension [2]. In this review, we present the genes involved in blood pressure regulation, and we discuss some associated syndromes.

Monogenetic Mineralocorticoid Hypertension Syndromes

The term of 'monogenetic mineralocorticoid hypertension' [3] refers to hypertension that results from a single genetic mutation causing excessive sodium resorption via the epithelial sodium channel (ENaC) in the distal tubule and collecting duct. This condition is characterized by suppressed plasma renin activity (PRA) as result

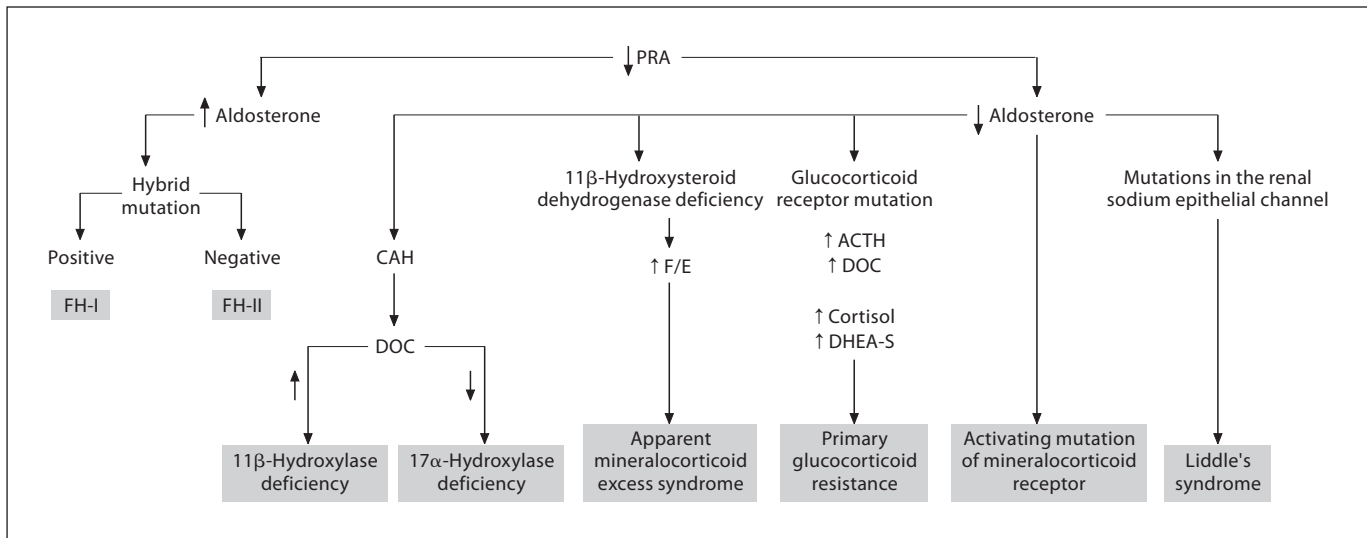


Fig. 1. Monogenetic mineralocorticoid hypertension syndromes. PRA = Plasma renin activity; FH = family hyperaldosteronism; CAH = congenital adrenal hyperplasia; DOC = deoxycortisol; F/E = cortisol/cortisone ratio.

of sodium retention, and it is associated with potassium and hydrogen ion wasting, which can lead to hypokalemia and alkalosis.

This type of hypertension can be accompanied by either excessive aldosterone production (associated with suppressed PRA) or suppressed aldosterone production (plasma aldosterone low or undetectable) (fig. 1, 2; table 1).

Conditions Associated with Excessive Aldosterone Production

Familial Hyperaldosteronism Type I (OMIM; #103900)

Glucocorticoid-remediable aldosteronism (GRA) is an autosomal dominant disorder characterized by hypertension, variable hyperaldosteronism, low PRA, normal or decreased serum potassium and abnormal adrenal steroid production, including 18-oxocortisol and 18-hydroxycortisol. It is caused by fusion of the cytochrome P450, subfamily XIB, polypeptide 1 gene (CYP11B1, 610613) and the cytochrome P450, subfamily XIB, polypeptide 2 gene (CYP11B2, 124080). The chimeric gene, in which the 5-prime regulatory sequences of the CYP11B1 gene were fused to the coding region of the CYP11B2 gene, results in an ectopic expression of aldosterone synthase in the zona fasciculata [4] that is regulated by ACTH. The diagnosis of glucocorticoid-remediable aldosteronism had been traditionally made using the dexamethasone suppression test; however, recent studies have shown that several patients with primary aldosteronism and a positive dexamethasone suppression test do not have the chimeric CYP11B1/CYP11B2 gene [5]. Plasma 18-hydroxycortisol determination by an ELISA method is reliable for detecting glucocorticoid-remediable aldosteronism, and it does so better than the dexamethasone suppression test [6]. Genetic testing by either Southern blot [7] or long polymerase chain reaction [8] techniques is sensitive and specific for GRA, and it should be performed in children or young adults with severe or resistant hypertension and a positive family history of early-onset hypertension and/or premature hemorrhagic stroke [9].

Table 1. Monogenetic mineralocorticoid hypertension syndromes

Familial hyperaldosteronism types I and II
Hypertensive forms of congenital adrenal hyperplasia
11β-Hydroxysteroid dehydrogenase deficiency
Liddle's syndrome
Activating mutation of mineralocorticoid receptor
Glucocorticoid resistance

GRA should be treated medically with a glucocorticoid to partially suppress pituitary ACTH secretion. In

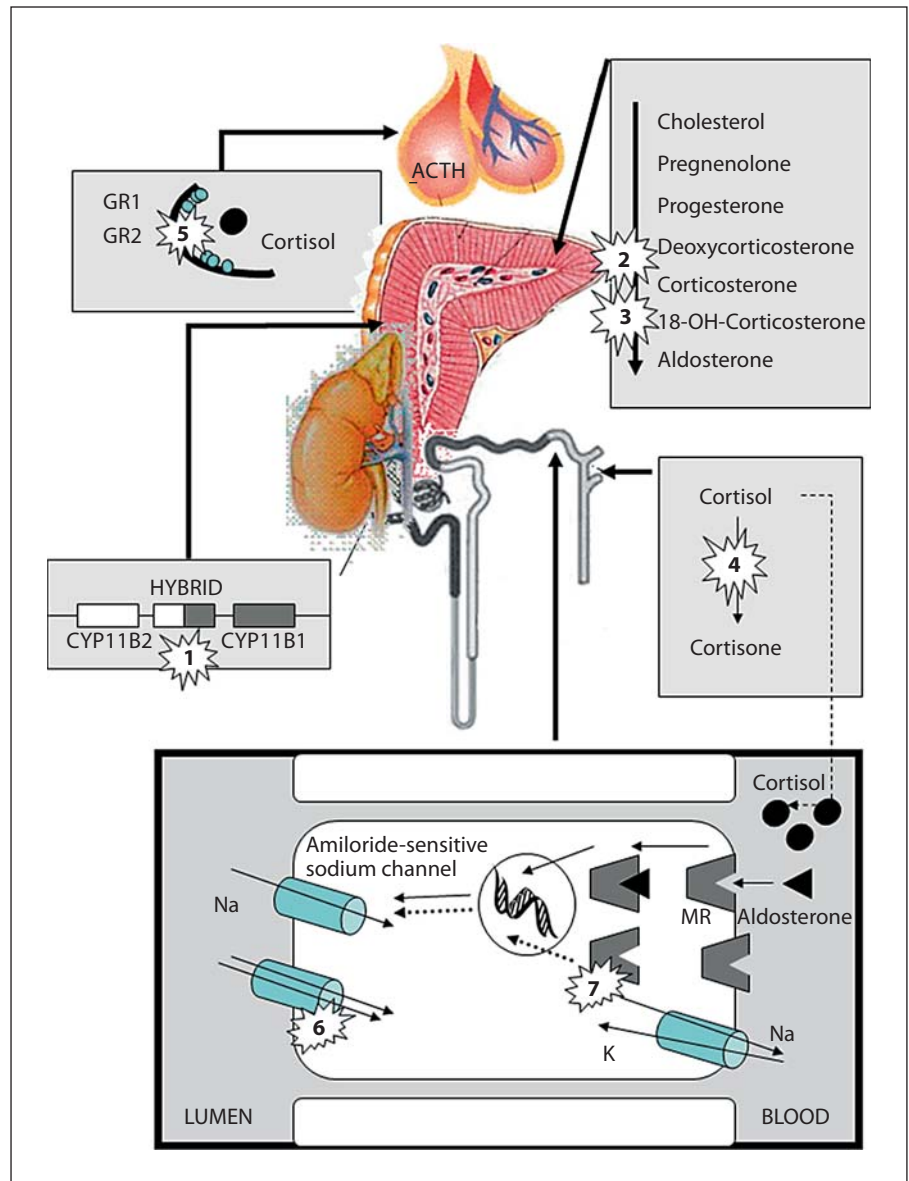


Fig. 2. Monogenic forms of mineralocorticoid hypertension syndromes. Some monogenic forms of mineralocorticoid hypertension syndromes are presented. Conditions associated with excessive aldosterone production: (1) familial hyperaldosteronism type I. Conditions not associated with excessive aldosterone production: (2) 11 β -hydroxylase deficiency; (3) 17 α -hydroxylase deficiency; (4) 11 β -hydroxysteroid dehydrogenase deficiency; (5) glucocorticoid resistance; (6) Liddle's syndrome, and (7) activating mutation of mineralocorticoid receptor.

general, the lowest possible dose of glucocorticoid that normalizes blood pressure and/or serum potassium concentration should be used [10]. Treatment with a glucocorticoid may not always normalize blood pressure, and addition of an MR antagonist should be considered in these cases [9].

Familial Hyperaldosteronism Type II (OMIM; #605635)

Familial hyperaldosteronism type II (FH-II) is a hereditary form of primary aldosteronism not attributable to the hybrid CYP11B1/CYP11B2 mutation that causes

GRA; it is characterized by hypersecretion of aldosterone due to adrenocortical hyperplasia, an aldosterone-producing adenoma (APA), or both. In contrast to familial hyperaldosteronism type I (OMIM; #103900), FH-II is not suppressible by dexamethasone. Although the exact mutation causing this syndrome has not been identified, different studies have associated a locus in chromosome 7p22 [11–13]. Normalization of aldosterone levels or aldosterone receptor blockade is necessary to prevent the morbidity and mortality associated with hypertension, hypokalemia, and cardiovascular damage. For more than four decades, the MR antagonist spironolactone has been

the agent of choice in the medical treatment of primary hyperaldosteronism. Esplerenone, a new MR antagonist agent, has been suggested. Although less efficacious than spironolactone amiloride, ENaC antagonists may be useful [9].

Although radiology plays no role in the initial diagnosis, CT and MR imaging have increasingly been used to diagnose APA. However, there is a wide variation in the reported diagnostic performance of CT (sensitivity 40–100%) and MR imaging (sensitivity 70–100%) in detecting APA [14].

Conditions Associated with Low or Undetectable Aldosterone

Hypertensive Forms of Congenital Adrenal Hyperplasia (OMIM; #202010 and 202110)

The most common hypertensive congenital adrenal hyperplasia (CAH) is due to a deficiency in 11 β -hydroxylase (#202010). It is present in 5–8% of all CAH cases, occurring in approximately 1–200,000 live births [15]. This type of CAH is an autosomal recessive disorder of corticosteroid biosynthesis resulting in androgen excess, virilization, and hypertension. It is caused by a mutation in the CYP11B1 gene, which encodes the 11 β -hydroxylase enzyme, which disrupts the conversion of 11-deoxycortisol to cortisol [15, 16]. Because of deficient cortisol production, the pituitary secretes large amounts of ACTH, stimulating adrenal steroidogenesis and increasing the plasma levels of 11-deoxycortisol, deoxycorticosterone and androgen precursors. Because deoxycorticosterone is an effective mineralocorticoid, excess causes retention of salt and water and suppression of the PRA and aldosterone, leading to hypertension. The disorder responds to suppressive doses of dexamethasone. Other hypertensive CAH is caused by a deficiency in 17 α -hydroxylase (#202110). This rare form of CAH is caused by defects in cytochrome P450c17, the single enzyme that has 17 α -hydroxylase and 17,20-lyase activities. This disorder is characterized by moderate arterial hypertension, suppression of the renin-angiotensin system, absent sex steroid synthesis, resulting in female external genitalia in 46,XY patients, and by impaired production of cortisol with a compensatory hypersecretion of ACTH. ACTH stimulates the synthesis of large amounts of deoxycorticosterone and corticosterone, leading to sodium reabsorption and suppression of PRA and SA [17]. The molecular genetic basis has been clarified in at least two dozen patients, identifying at least 17 different lesions in the

P450c17 gene [18–20]. Patients affected may also be treated with suppressive doses of dexamethasone or physiologic doses of hydrocortisone during childhood.

11 β -Hydroxysteroid Dehydrogenase Deficiency (OMIM; #218030)

This syndrome is the result of impaired activity of the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2). This enzyme is expressed in mineralocorticoid target tissues and is crucial in the kidney, where it normally inactivates cortisol by converting it to cortisone [17, 21]. Thus, when there is congenital absence of 11 β -HSD2 [22–24], the protective mechanism fails, and cortisol gains inappropriate access to the mineralocorticoid receptor (MR), whose affinity to cortisol is equal to that of aldosterone [25, 26]. Because the cortisol secretion is nearly 1,000 times higher than that of aldosterone in affected patients, cortisol saturates the MR. The excess cortisol binding produces a hypermineralocorticoid state, which results in hypokalemia, sodium retention and volume expansion, thus suppressing plasma renin and aldosterone secretion. This syndrome is characterized by a high plasma cortisol/cortisone ratio or a high urine tetrahydrocortisol/tetrahydrocortisone ratio that is almost 10 times higher than normal [27]. Although the plasma cortisol half-life is increased, elevated serum cortisol concentrations are not typically present and do not aid in the diagnosis. In patients with congenital absence of 11 β -HSD2, homozygous inactivating mutations have been identified in more than 20 cases [27–29]. The disorder is inherited as an autosomal recessive trait, and most heterozygous individuals have a normal phenotype. Recently, we looked for the possible contribution of a decreased 11 β -HSD2 activity in the pathogenesis of low-renin hypertension, and we found that low-renin essential hypertensives had increased serum cortisol/cortisone ratios as compared with normotensive subjects. This suggests that some essential hypertensives with suppressed renin activity may have an impairment in the cortisol inactivation catalyzed by the enzyme 11 β -HSD2 [30]. This type of hypertension responds to spironolactone administration or a low sodium diet, suggesting that it is mediated by the mineralocorticoid (type I) receptor. Administration of cortisol or of ACTH exacerbates the hypertension.

Glucocorticoid Resistance (OMIM; #138040)

Glucocorticoid resistance is a rare condition characterized by generalized, partial, target-tissue insensitivity to glucocorticoids. Compensatory elevations in circulat-

ing adrenocorticotrophic hormone (ACTH) concentrations lead to increased secretion of cortisol and adrenal steroids with mineralocorticoid and/or androgenic activity, but without any clinical evidence of hypercortisolism. The clinical spectrum of the condition is broad, ranging from asymptomatic to severe cases of hyperandrogenism, fatigue and/or mineralocorticoid excess. The molecular basis of glucocorticoid resistance has been ascribed to mutations in the human glucocorticoid receptor gene, which impair glucocorticoid signal transduction, thereby altering tissue sensitivity to glucocorticoids [31]. Genetic studies have documented that mutations and polymorphisms at the GR gene might be associated with different metabolic syndromes, such as glucocorticoid resistance, glucocorticoid sensitivity, obesity, and hypertension [14]. The differential diagnosis should be done with Cushing disease.

Liddle's Syndrome (OMIM; #177200)

Liddle's syndrome is caused by mutations in the subunits of the renal sodium epithelial channel [32–34]. The amiloride-sensitive epithelial channel is considered the rate-limiting step for sodium absorption in the distal nephron, and it is composed of three subunits named α , β and γ [35, 36]. In Liddle's syndrome, mutations have been found in the β and γ subunits. Because of these mutations, a constitutive activation of the epithelial channel leads to increased sodium absorption and volume expansion. This disorder is inherited as an autosomal dominant disorder in which affected patients present with hypertension, suppressed PRA, and low aldosterone levels. The defect in the sodium channels of the distal nephron results in excessive salt absorption and potassium wasting. ENaC also has been implicated as a candidate gene for the development of essential hypertension. A potentially polymorphic repetitive region (GT dinucleotide short tandem repeat [STR]) was identified in intron 8 of β -ENaC gene (SCNN1B). We have identified a polymorphic GT-STR in the β -ENaC gene that is present in patients with essential hypertension and normotensive patients in the Chilean population. Biochemical analysis showed a possible linkage between this polymorphic region and hypertension characterized by low renin. An in vitro assay has suggested that GT-STR could regulate β -ENaC expression [37]. A genetic analysis of the amiloride-sensitive ENaC is recommended in assessing patients with low-renin, salt-sensitive hypertension whose blood pressure is not responsive to spironolactone treatment [38]. This disorder responds to inhibitors of epithelial sodium transport, e.g., triamterene [39]. Affected patients also re-

spond to renal transplantation, which results in normalization of blood pressure and of electrolyte abnormalities.

Activating Mutation of Mineralocorticoid Receptor (OMIM; #605115)

This disorder can be caused by mutation in the MR gene in the locus 4q31.1 (OMIM; 600983). A gain of function mutation resulting in the substitution of leucine for serine at codon 810 (S810L) in the human MR (MR) is responsible for early-onset hypertension that is exacerbated in pregnancy. All steroids, including progesterone, that display antagonist properties when bound to the wild-type MR are able to activate the mutant receptor (MR(L810)). These findings suggest that progesterone may contribute to the dramatic aggravation of hypertension in MR(L810) carriers during pregnancy. However, the steroid(s) responsible for hypertension in MR (L810) carriers (men and nonpregnant women) has not yet been identified [40].

Genes Contribute to the Phenotype of Essential Hypertension

Angiotensin is formed from a precursor, angiotensinogen, which is produced by the liver and found in the α -globulin fraction of plasma. Renin cleaves from angiotensinogen a terminal decapeptide, angiotensin I. This is further altered by the enzymatic removal of a dipeptide to form angiotensin II. Angiotensin II is an important effector controlling blood pressure and volume in the cardiovascular system. Angiotensin II interacts with two different subtypes of cell surface receptors, types 1 and 2 (OMIM; AGTR2, 300034). Type 1 receptors seem to mediate the major cardiovascular effects of angiotensin II.

Angiotensinogen (OMIM; #106150)

Caulfield et al. [41] investigated linkage between the angiotensinogen (AGT) gene locus to essential hypertension in the 63 multiplex families. This linkage was consistently maintained in the subgroup of subjects with diastolic pressure >100 mm Hg and in the subgroups classified according to gender, providing strong and consistent support for the linkage of regions within or close to the AGT gene to essential hypertension.

Molecular variants in the AGT gene, including M235T, T174M, and a mutation in the promoter region that involves the presence of an adenine (A) instead of a guanine (G) 6 bp upstream from the transcription initiation site

(G-6A), have also been reported to have a positive correlation with hypertension [42]. Of the molecular variants of AGT that have been identified, a significant association with hypertension was observed with 2 amino acid substitutions, M235T and T174M. Additionally, in an ethnically homogeneous population of Japanese patients, T235 was associated with essential hypertension [43]. Thus, ethnicity may make a significant difference in the role of various genes in certain complex traits [44]. We demonstrated that there is a high prevalence of the T235 variant in our Hispanic population. The slight difference that we found between the prevalence of the T235 variant in hypertensive and normotensive subjects was not statistically significant and did not permit us to establish an association between the T235 variant and essential hypertension [45]. Recently, the interaction among G-6A, M235T and T174M polymorphisms in combinations or haplotypes was significantly associated with a high plasma aldosterone concentration and low PRA, suggesting that these interactions are associated with low-renin hypertension [46].

Angiotensin I-Converting Enzyme (OMIM; #106180)

The angiotensin converting enzyme (ACE) or kinase II is a dipeptidyl carboxypeptidase that plays an important role in blood pressure regulation and in electrolyte balance by hydrolyzing angiotensin I into angiotensin II, a potent vasopressor, and aldosterone-stimulating peptide. The enzyme is also able to inactivate bradykinin, a

potent vasodilator. The insertion/deletion ACE polymorphism (ACE I/D) regulates different levels of circulating and tissue ACE activities, which may induce diverse adrenergic responses to physiological stimuli. The presence of the D allele on the ACE gene in middle-aged hypertensive patients determines higher circulating ACE activity, but not increased sympathetic activity, in response to submaximal exercise [47].

Angiotensin Receptor-1 (OMIM; #106165)

The vasopressor angiotensin II regulates vascular contractility and blood pressure through binding to type 1 angiotensin II receptors. Two subtypes of angiotensin II type 1 receptors, 1A (AGTR1A) and 1B (AGTR1B), have been identified in human, rat, and mouse. The AGTR1A and AGTR1B share substantial sequence homology and wide tissue distributions [48]. Variants in the human AGTR1A gene may affect blood pressure in the human [49].

In summary, mineralocorticoid hypertension should be suspected in patients with an early onset of hypertension in the presence of a strong family history of hypertension associated with low PRA, with or without hyperaldosteronism. Clinical manifestations, plasma or urinary steroid tests, and imaging tests can aid in the diagnosis of some patients with this syndrome. However, genetic tests, which are available in some tertiary references centers, allow an accurate and definitive diagnosis.

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